REMARKS

Claim 1 is Not Obvious over Kikuchi

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi *et al.* (US 2004/0022848, "Kikuchi"). (Pages 2-3 of the Office Action). Applicant respectfully traverses the rejection.

In *KSR International Co. v. Teleflex Inc.*, the U.S. Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385, 1395 (2007) (emphasis added). According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, the guidelines for the examination of patents in the wake of the *KSR* decision make clear that an Examiner may still apply the TSM test, after resolution of the *Graham* analysis. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57528 (Oct. 10, 2007) ("USPTO Guidelines").

The *Graham* factual inquiries are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR,* 82 U.S.P.Q.2d at 1395 (*citing Graham,* 383 U.S. at 15-17). Once the *Graham* factors have been addressed, the Examiner may apply the TSM test, asking whether (1) a teaching, suggestion or motivation exists in the prior art to combine the references cited, and (2) one skilled in the art would have a reasonable expectation of success. *See* USPTO Guidelines at 57534.

The Office Action states that Kikuchi et al. teach a pharmaceutical preparation obtained by primary granulation of a drug and a hydrophobic additive (waxy substance) (paragraphs 0061 and 0062), followed by secondary granulation of the obtained granules by wet granulation using a hydrophobic wet granulation material (see paragraph 0065). (Page 2 of the Office Action). Applicant respectfully traverses this rejection.

Claim 1 recites sustained-release preparations, which are prepared from double granules obtained by primary granulation of drug according to melt granulation using

hydrophobic release-delaying additives, and then by secondary granulation of the obtained granules according to wet granulation using hydrophobic wet-granulation material.

On the contrary, the compositions of Kikuchi are prepared by spray granulation method using synthetic aluminium silicate and/or hydrous silicon dioxide (Kikuchi, paragraph [0004]). Although Kikuchi mentions a secondary granulation, it does not use hydrophobic materials, but hydrophilic materials such as erythritol and D-sorbitol. See, paragraph [0065] and [0085]. Kikuchi further discloses that a secondary granulation may be accomplished by melting granulation [paragraph 0065].

Thus, Kikuchi, which uses melting granulation and hydrophilic materials, does not disclose or suggest the preparation of instant claim 1 reciting wet granulation and hydrophobic materials. Kikuchi is missing teaching or suggestion of essential elements of the claimed invention. Kikuchi fails to suggest or motivate the preparations obtained by the wet granulation using hydrophobic material as recited in claim 1.

Because the preparations of instant claim 1 require wet granulation using hydrophobic materials as a secondary granulation, the present invention (1) minimizes the amount of hydrophobic additives, (2) imparts sustained-releasing property, (3) eliminates adhesion of granules occurring during tablet preparation, and (4) allows the production of a tablet easy and convenient (paragraph [0009]).

On the contrary, by the melting granulation disclosed in Kikuchi, the sustained-release preparations of the present invention cannot be achieved. As shown in Experimental example 1 of the present application, the preparation of Comparative example 1 has only the surface formed by melting granulation as in Kikuchi, and it exhibits serious adhesion in spite of addition of excessive amount of lubricant, making the tablet preparation impossible (paragraph [0032] of the present publication).

Therefore, Kikuchi, which uses melting granulation as a secondary granulation, teaches away from the sustained-release preparations of the present invention. For purpose of obviousness analysis, a prior art that teaches away negates a motivation to modify the prior art to meet the claimed invention. Thus, Kikuchi does not provide one skilled in the art with any suggestion or motivation for the claimed sustained-release preparations.

Further, Kikuchi uses synthetic aluminium silicate and hydrous silicon dioxide to prevent adhesion of the granulated product onto the inside of a spray granulation apparatus (Kikuchi, paragraph [0004]). Thus, the technical solution used in Kikuchi is "to add synthetic aluminium silicate and hydrous silicon dioxide," but not "secondary granulation" as

in the present invention. In contrast to Kikuchi, the present invention minimizes the amount of hydrophobic additives for imparting sustained-releasing property (paragraph [0009]). Thus, Kikuchi does not provide to one skilled in the art any suggestion or motivation to select secondary granulation as recited in present claim 1.

In addition, Kikuchi does not teach or suggest the sustained-release preparation of the present invention. Example 2 of Kikuchi describes that the formed granules exhibited excellent drug release property upon dissolution (*i.e.,* substantially complete release of the drug within 30 minutes). See, paragraph [0081]. Because Kikuchi focuses on fast release, it teaches away from the sustained-release preparations of the present invention, and does not suggest that the present invention would have a reasonable expectation of success.

In sum, Kikuchi provides no teaching, suggestion or motivation to one skilled in the art for the sustained-release preparations of claim 1. From Kikuchi which teaches away from the instant claim, one skilled in the art would have no reasonable expectation of success. Thus, instant claim 1 is not obvious by Kikuchi.

There are sufficient unexpected results to rebut even a *prima facie* case of obviousness.

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited reference, there is evidence of unexpected or superior results for the sustained-release preparations of the present invention to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *see also In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004).

In this regard, Applicant invites the Examiner's attention to the dissolution and adhesion tests for the sustained-release preparations of the present invention, and Declaration by one of the inventors (Dr. KIM, Jung Ju) under 37 C.F.R. § 1.132 ("Declaration") filed concurrently herewith.

As evidenced by Dr. KIM's Declaration and discussed below, the sustained-release preparations of the present invention showed superior and unexpected results in the tests. Such results must be considered in determining unobviousness of the claimed inventions.

To prove superiority of the claimed invention, the following tests described in the specification (Example 13) were conducted by one of the inventors (Dr. Kim, Jung Ju) and his colleagues at AMOREPACIFIC R&D Center, the assignee of the application, to compare with preparations 1 and 2 of Kikuchi.

Table 1: Test preparations

Ingredient (mg)	Kikuchi Preparation 1	Kikuchi Preparation 2	Example 13 of the present invention
Tramadol hydrochloride	150	150	150
Hydrogenated castor oil	150	150	150
Synthetic aluminum silicate	3.8	3.8	-
Hydroxypropylmethylcellulose	58.4	-	-
Glycerin monostearate	-	58.4	-
Ethylcellulose	-	-	62.2
Talc	10.2	10.2	10.2
Magnesium stearate	7.6	7.6	7.6
Total	380	380	380

Example 13 of the present application

According to the method described in the specification of the present application, a mixture of hydrogenated castor oil and tramadol hydrochloride was heated to 75°C and mixed until hydrogenated castor oil is softened. This was cooled to normal temperature to form solid mass; and the mass was pulverized and screened with 20 mesh, to prepare primary granules. The primary granules were mixed with ethylcellulose and subjected to secondary wet granulation. The granules were dried, mixed with talc and magnesium stearate, compressed to adequate form to prepare tablets.

Preparations 1 and 2 of Kikuchi

Two pharmaceutical preparations according to Kikuchi et al were prepared. Primary granulations of Kikuchi Preparations 1 and 2 were processed according to Kikuchi et al. (paragraph 0061) by using hydrogenated castor oil as a hydrophobic additive (waxy substance), melting it, mixing with synthetic aluminum silicate and tramadol hydrochloride, and then spraying to prepare primary granules.

The Office Action points out "paragraph 0065" of Kikuchi et al., for secondary granulation of the obtained granules by wet granulation using a hydrophobic wet granulation material. (Page 2 of Office Action). Kikuchi et al. discloses in paragraph 0065 as follows:

(A) Secondary granulation may be accomplished by wet fluidized bed granulation, wherein a binder solution such as a solution of hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, or sorbitol is used.

(B) Alternatively, secondary granulation may be accomplished by melting granulation, wherein a low-melting-point substance such as polyethylene glycol or glycerin monostearate is used as a binder.

Therefore, secondary granulation of Kikuchi Preparations 1 was processed by wet granulation with the above primary granules and hydroxypropylmethylcellulose. Secondary granulation of Kikuchi Preparations 2 was processed by mixing glycerin monostearate with the above primary granules, heating the mixture and then granulation. The granules were dried, mixed with magnesium stearate, and compressed to adequate form to prepare each tablet. The primary granules of Kikuchi Preparation 2 were prepared by using same amount of same granulating substance with those of Example 13 of the present invention.

Test for effect on surface adhesion

In case of Example 13 of the present invention, adhesion property of the surface of the primary melt granules was covered through secondary wet granulation, thus adhesion toward punch or die was not observed during tablet process. The granules prepared in Kikuchi Preparation 2 exhibited serious adhesion in spite of secondary granulation (melt granulation), resulting in impossibility of tablet preparation.

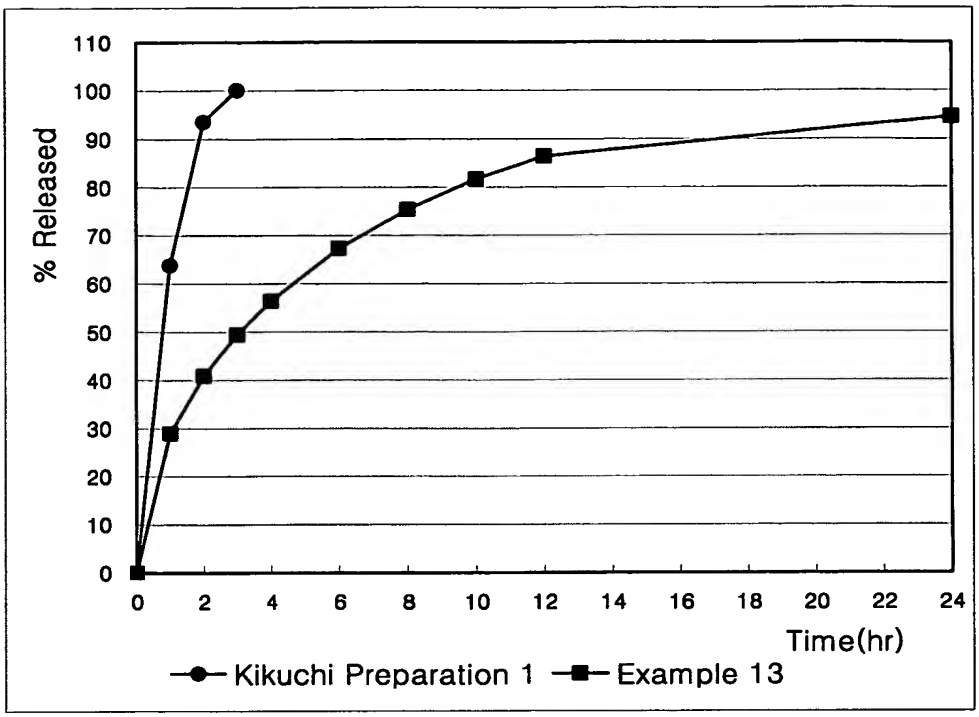
In case of Kikuchi Preparation 1, the granules were prepared by secondary wet granulation with hydroxypropylmethylcellulose, which is not waxy, but hydrophilic. They were compressed easily into tablet without adhesion, like ones of Example 13 of the present invention.

Dissolution test

The tablet was prepared in accordance with Example 13 of the present invention and Kikuchi Preparation 1. Release tendency of tablets of the above two preparations was observed by using USP dissolution test device. Time-dependent dissolution rate of drug was determined under the test condition (simulated intestinal solution (Solution II, pH 6.8), paddle type II, 50 rpm/900ml), and result is represented in the following Table 2.

Table 2.

Time (hr)	% Released	
	Kikuchi Preparation 1	Example 13 of the present invention
0	0.00	0.00
1	63.8	28.99
2	93.5	40.90
3	100.1	49.43
4	-	56.33
6	-	67.29
8	-	75.40
10	-	81.68
12	-	86.39
24	-	94.59



In the above dissolution test result, it was confirmed that, in case that tablets were prepared by primary melt granulation with way material and then by secondary wet granulation with hydrophilic material such as hydroxypropylmethylcellulose according to Kikuchi et al., drug releases more rapidly, than ones prepared by secondary wet granulation with hydrophobic material of Example 13 of the present invention. Especially, in case of freely soluble drug such as tramadol hydrochloride, external water penetrates easily into the internal of tablet due to hydroxypropylmethylcellulose, which is hydrophilic secondary wet granulation material. Through the water channel formed, the drug was dissolved rapidly, and then released from the tablet. Furthermore, since the middle of the drug-release, the preparation is disintegrated due to the dissolution of hydroxypropylmethylcellulose itself, and then the primary granules are separated and scattered. Eventually, the increase of the surface area of drug- release is induced and the drug releases very rapidly.

On the other hand, in case of the preparation according to the present invention, external water cannot penetrate easily into the internal of tablet due to secondary wet granulation material of hydrophobic property. The drug is dissolved slowly from the surface of the preparation, thereby water channels are formed continuously and then the drug can be released through the channels. Therefore, until the drug-release is completion, the whole shape of the preparation is maintained and only the drug is released from the preparation.

Thus, the preparation according to the present invention shows the excellent sustained release effect. The present invention was conceived to resolve the problems of the conventional techniques, and its object lies in minimizing the amount of hydrophobic additives for imparting **sustained**-releasing property, and eliminating adhesion phenomenon of granules occurring during the tablet preparation, thereby allowing the production of tablet to be easy (specification [9]).

In sum, the above superior effects of the present invention are sufficient to rebut even a *prima facie* case of obviousness. In view of these unexpected results, the instant claim is not obvious. *See In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 1-7 are Not Obvious over Kikuchi in View of Oshlack

Next, Claims 1-7 are rejected under 35 U.S.C 103(a) as being unpatentable over Kikuchi in view of Oshlack et al. (US 2002/0102302, "Oshlack"). (Pages 3-5 of the Office Action). It is alleged that Oshlack et al. teach a sustained release composition comprising tramadol (paragraph 0014), waxes (paragraph 0056), beeswax (paragraph 0056), hydrogenated vegetable oil (paragraph 0056), and additives (paragraph 0021), and therefore, it would have been obvious to a person of ordinary skill in the art to disclose a sustained release pharmaceutical preparation comprising tramadol and using two granulation processes, as taught by Kikuchi et al. in view of Oshlack et al. (Office Action, pages 4-5). Applicant respectfully traverses the rejection.

As discussed above, Kikuchi fails to suggest or motivate the preparations obtained by the wet granulation using hydrophobic material as recited in claim 1. Oshlack does not cure the deficiency of Kikuchi.

Oshlack relates to a stabilized sustained release oral solid dosage form containing tramadol as an active agent. However, Oshlack, alone or in combination with Kikuchi, fails to disclose or suggest the preparations obtained by the wet granulation using hydrophobic material as recited in claims 1-7. In Oshlack, the formulations are prepared via a melt extrusion/granulation technique. In Oshlack, the invention is to obtain formulations from which active ingredient can be released almost completely after curing process and release rate may be not changed during storage. Thus, Oshlack fails to teach or suggest essential elements of wet granulation using hydrophobic material in the claimed invention.

For example, paragraph [0004] of Oshlack discloses that the agents (e.g., waxes) used in sustained release dosage formulations often present problems of physical stability during storage because they undergo physical alterations on prolonged standing. To solve such problems, in Oshlack, the dosage form is cured at a suitable temperature, until an endpoint is reached at which the cured dosage form, when subjected to in-vitro dissolution, releases the tramadol in amounts which do not vary at any time point along the dissolution curve by more than about 20% of the total amount of tramadol released, when compared to the in-vitro dissolution of the formulation prior to curing. (paragraph [0018] and Claim 1). Therefore, Oshlack does not even teach or suggest any preparations obtained by the wet granulation using hydrophobic material of the present invention.

In view of the foregoing, neither Kikuchi nor Oshlack, alone or in combination, teaches or suggests the claimed sustained-release preparations. Nowhere does Kikuchi or Oshlack suggest or motivate to select the wet granulation using hydrophobic material. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success from Kikuchi and Oshlack. A *prima facie* case of obviousness has not been established and the rejection must be withdrawn.

The unexpected results rebut even a *prima facie* case of obviousness.

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, there is evidence of unexpected or superior results for the sustained-release preparations of the present invention to rebut a *prima facie* case of obviousness. As the Examiner is well aware, such unexpected results can rebut even a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *see also In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004).

To prove the unexpected results of the present invention over Kikuchi et al. in view of Oshlack et al., the following experiment was conducted by the inventor (Dr. Kim, Jung Ju) and his colleagues at AMOREPACIFIC R&D Center, the assignee of the application.

Table 3: Test preparations

Ingredient (mg)	Preparation K&O	Example 13 of the present invention
Tramadol hydrochloride	150	150
Hydrogenated castor oil	150	150
Ethylcellulose	62.2	62.2
Talc	10.2	10.2
Magnesium stearate	7.6	7.6
Total	380	380

Example 13 of the present invention

The primary granules were mixed with ethylcellulose and subjected to secondary **wet** granulation. The granules were dried, mixed with talc and magnesium stearate, and compressed to adequate form to prepare tablets.

Preparation of Kikuchi and Oshlack ("K&O")

A mixture of hydrogenated castor oil and tramadol hydrochloride was heated to 75°C and mixed until hydrogenated castor oil softened. This was cooled to normal temperature to form solid mass; and the mass was pulverized and screened with 20 mesh, to prepare primary granules. Secondary granulation was processed by mixing ethylcellulose with the above primary granules, and subjected to heating the mixture to proceed the melt granulation.

Test for effect on surface adhesion

The primary granules of Preparation K&O were prepared according to the same method by using same amount of same granulating substance with those of Example 13 of the present application.

In case of Example 13, adhesion property of the surface of the primary melt granules was covered through secondary **wet** granulation, thus adhesion toward punch or die was not observed during tablet process, while the granules prepared in Preparation K&O exhibited serious adhesion.

Preparation K&O showed serious problems in actual production, i.e. reduced flow of particles at hopper, severe adhesion to punch or die at the time of tablet compression and increased resistance at the time of removing tablet from tablet presses, resulting in impossibility of tablet preparation. During tablet process, the adhesion to punch or die induces irregular hole-formation in the surface of the tablet, resulting in a large variation of tablet weight and an irregular drug-release. For sustained-release preparation, the irregular drug-release cannot be accepted because it relates to fatal adverse effect. The adhesion phenomena occur very seriously in the continuous tablet process.

The above test results show that, although secondary granulation is conducted with hydro**phobic** material, in case of secondary **melt** granulation as in the cited art, adhesion property of the surface of the primary melt granules **cannot** be covered through the second granulation. Only in case of secondary **wet** granulation according to the present invention, adhesion property of the surface of the primary melt granules **can** be covered through second granulation.

In sum, the unexpected effects of the present invention are sufficient to rebut even a *prima facie* case of obviousness. In view of these unexpected results, the instant claims are not obvious. *See In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

The Double Patenting Rejection Should Be Withdrawn

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 11/572,326. (Office Action, pages 5-6).

Solely to promote prosecution and without prejudice, a terminal disclaimer can be submitted in Application No. 11/572,326 in due course. In any event, Applicants respectfully request that the rejection be held in abeyance until the claims of the present application are deemed otherwise allowable. Thus, Applicant respectfully requests that this double patenting rejection be withdrawn.

Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

Date: January 23, 2008

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